

REMARKS

Amendments to the Claims

Claims 15, 16, 23, 45, 46, and 53 were amended to insert the Sequence ID No. for the amino acid sequence.

Independent claims 1, 12 and 13 were amended to define the size of the polymeric carrier-conjugate as greater than about 6 nm. This is described in the specification at least at page 9, lines 12-19, which states that “consistent with this features, macromolecules with sizes above about 6 nm (MW about 50,000 Da) exhibit marked renal clearance. Accordingly, in certain embodiments the polymeric carrier may be designed to be greater than this renal exclusion limit.”.

Claim Objections

Claims 50 and 53 were objected to for depending upon rejected claims, but as otherwise allowable. However, the Examiner indicated that the claims would be allowable if rewritten to overcome the rejections made by the Examiner under 35 U.S.C. §112 and second paragraphs, and to include all of the claim limitations of the base claim and any intervening claims.

Rejection Under 35 U.S.C. § 112, first paragraph – written description

Claims 1-6, 9-23, 29, 33, 39, 43-49, 51-52 and 54-56 were rejected under 35 U.S.C. §112 as failing to comply with the written description requirement. Applicants respectfully traverse this rejection. Claim 4 has been cancelled.

Specifically, the Examiner alleged that while there is written support for the specific oligopeptide linker IPVGLIG cleavable by MMP-2, there is no written support for oligopeptide linkers that are cleavable by serine proteases. This appears to be an error since the specification clearly provides support for a number of different linkers. **Applicants respectfully direct the Examiners attention to the specification at least at page 16, lines 15-16, which states that cleavage motifs for a number of proteases are known.** As previously stated, these sequences are known in the art (see for example, Kridel, et.al. *J. Biol. Chem.*, 277: 23788-93 (2002) (a copy of which is attached), disclosing a list of oligopeptide sequences for targeting release by the cleavage of MT1-MMP, but not MMP-2 and MMP-9 in Table 1; a large database summarizing the cleavage motifs is available online (<http://merops.sanger.ac.uk/>), which has been in existence since 1996. **Moreover, the Examiner's attention is drawn to Table 1 in Appendix A, which discloses a number of oligopeptide sequences for targeting various tumor-associated proteases. Included in this list are examples of serine proteases, metalloproteases, and cysteine proteases. The Examiner's attention is also drawn to Table 1 in Turk et al., *Nature Biotechnology*, 19:661-667 (2001) ("Turk"), a copy of which is attached, cited in the present application at least at page 33, line 5, disclosing cleavage motifs for various matrix metalloproteinases.**

Thus, the specification has satisfied the requirement for a description of a representative number of species. The written description requirement does not require a description of the complete structure of every species within a chemical genus. (see *Utter v. Hiraga*, 845 F.2d 993,

998, 6 U.S.P.Q.2d 1709, 1714 (Fed. Cir. 1988), stating “A specification may, within the meaning of 35 U.S.C. §112, para. 1, contain a written description of a broadly claimed invention without describing all species that claim encompasses.”). All that is required is that the specification provides sufficient description to reasonably convey to those skilled in the art that, as of the filing date sought, the inventor was in possession of the claimed invention. *Union Oil of California v. Atlantic Richfield Co.*, 208 F.3d 989, 997, 54 U.S.P.Q.2d 1227, 1232 (Fed. Cir. 2000); *Vas Cath*, 935 F.2d at 1563-64.

The Examples in the present application include conjugates which have selective drug release mediated by matrix metalloproteinase-2 (MMP-2) and -9 (MMP-9).

With respect to claim 2, the Examiner alleged that while there is support for a plurality of drugs for use in the drug conjugate there is no written support that more than one type of linker may be used on the same drug conjugate. The Examiner’s attention is respectfully drawn to original claim 2, which recited additional linkers. An original claim is part of the specification. Furthermore, as stated discussed above with respect for there is adequate support for linkers for digestive enzyme is selected from the group consisting of serine proteases and matrix metalloproteinases as recited in claims 1 and 2.

For at least the reasons set forth above, claims 1-3, 5, 6, 9-23, 29, 33, 43-49, 51-52 and 54-56 satisfy the written description requirement.

Rejection Under 35 U.S.C. § 112, first paragraph- enablement

The Examiner alleged that claims 1-6, 9-23, 29, 33, 39, 43-49, 51-52, and 54-56 are not enabled. Applicants respectfully traverse this rejection as applied to the amended claims.

Legal Standard for Enablement

The standard for enablement is whether one of ordinary skill in the art can make and use that which is claimed without undue specification. There is no requirement for working examples nor must each and every embodiment be enabled. Moreover, once the applicant has presented evidence to rebut the examiner's rejection, the rejection cannot be sustained in the absence of evidence, *not mere allegation*, on the part of the examiner.

The Court of Appeals for the Federal Circuit (the Federal Circuit) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art, without undue experimentation. *See, e.g., Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365, 42 U.S.P.Q.2d 1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993); *See also In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (CCPA 1970); *United States v. Teletronics, Inc.*, 857 F.2d 778, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988); *In re Stephens*, 529 F.2d 1343, 188 U.S.P.Q. 659 (CCPA 1976). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *M.I.T. v. A.B. Fortia*, 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed. Cir. 1985). In addition, as affirmed by the Federal Circuit in *Spectra-*

Physics, Inc. v. Coherent, Inc., 827 F.2d 1524, 3 U.S.P.Q.2d 1737 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well-known in the art.

Whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. See *In re Wands*, 858 F.2d 731, 735, 736-737, 8 U.S.P.Q.2d 1400, 1402, 1404 (Fed. Cir. 1988). A determination of undue experimentation is a conclusion based on weighing many factors, not just a single factor. Many of these factors have been summarized in *In re Forman*, 230 U.S.P.Q. 546, 547 (Bd. Pat. App. & Int. 1986) and are set forth in *In re Wands*. They are: (1) The quantity of experimentation necessary (time and expense); (2) The amount of direction or guidance presented; (3) The presence or absence of working examples of the invention; (4) The nature of the invention; (5) The state of the prior art; (6) The relative skill of those in the art; (7) The predictability or unpredictability of the art; and (8) The breadth of the claims. The M.P.E.P. explains that "[i]t is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others." (M.P.E.P. § 2164.01 (a)). Thus, a conclusion of nonenablement must be based on the evidence as a whole, as related to these factors. (*Id.*)

In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation "must not be

unduly extensive.” *Atlas Powder Co., v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 U.S.P.Q. 409, 413 (Fed. Cir.1984).

As noted in *Ex parte Jackson*, the test is not merely quantitative, since a considerable amount of experiment is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed. *Ex parte Jackson*, 217 U.S.P.Q. 804, 807 (Bd. Pat. App. & Int. 1982).

There is no requirement for examples. *In re Borkowski*, 422 F.2d 904, 164 U.S.P.Q. 642 (C.C.P.A. 1970). Further, patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

The first paragraph of Section 112 provides that the “specification shall contain a written description of the invention...” 35 U.S.C. § 112 (2005). “The description requirement’s purposes are to assure that the applicant was in full possession of the claimed subject matter on the application filing date and to allow other inventors to develop and obtain patent protection for later improvements and subservient inventions that build on applicant’s teachings.” 3-7 Chisum on Patents § 7.04 (2005), citing *Fields v. Conover*, 443 F.2d 1386, 170 U.S.P.Q. 276 (CCPA 1971).

Analysis

The test for enablement is whether one of ordinary skill in the art could make and use the claimed compositions and methods without *undue* experimentation. Whether or not experimentation is undue is a conclusion based on weighing *many* factors, not just a *single* factor, as presented by the Examiner. There is no requirement that all embodiments within a genus be enabled to meet the standard for enablement.

A proper analysis of the *Wands* factors shows that the claimed compositions and methods are enabled. As discussed in detail below, based on the amount of guidance provided in the specification, the quantity of experimentation necessary, the presence of working examples, and the breadth of the claims, one of ordinary skill in the art would be able to make and use the claimed compositions without undue experimentation.

The breadth of the claims

The claims are directed to a conjugate containing a polymeric carrier, a drug molecule, and a linker that includes a first and a second end, wherein the linker includes an oligopeptide recognition segment that is cleaved when the conjugate is exposed to a digestive enzyme. The linker is limited to those linkers, which contain an oligopeptide recognition segment that is cleaved by a digestive enzyme selected from serine proteases and matrix metalloproteinases.

The Examiner alleged that the claims are very broad and fail to provide guidance on other types of linkers or what structural characteristics should be present to give a linker cleavable functionality. Applicants respectfully disagree and draw the Examiner's attention to additional

cleavable sites for the digestive enzymes recited in the claims disclosed in Table I Appendix A of the present specification, and to Turk cited in the present application, both of which are discussed in detail below.

The state of the prior art

In the Office Actions mailed March 21, 2007 and September 28, 2007 and March 5, 2008, the Examiner alleged that the state of the art of drug conjugates comprising peptide linkers is high; while the state of the art for using any peptide linkers cleavable by digestive enzymes is very low or does not exist. The Examiner asserts that this is verified by applicants' own specification which states "a digestive enzyme that cleaves oligopeptides will typically exhibit strong selectivity for oligopeptides that include one or a small subset of amino acid sequences called recognition sequences". Applicants' respectfully disagree.

As discussed above in response to the written description rejection, the specification discloses linkers that can be cleaved by digestive enzymes recited in the claims. Additionally, such linkers are known in the art and the specification cites several references which disclose methods for determining cleavage motifs for digestive enzymes, such as substrate phase display libraries (Matthew and Wells, *Science*, 260:1113 (1993)); position scanning peptide libraries (Rano *et al.*, *Chem. Biol.*, 4:149 (1996)); and mixture-based peptide libraries (Turk *et al.*, *Nature Biotechnology*, 19:661 (2001)) (page 17, lines 1-17) for those enzymes for which the cleavage sequences are not known.

As noted in *Ex parte Jackson*, the test for enablement is not merely quantitative, since a considerable amount of experiment is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed. *Ex parte Jackson*, 217 U.S.P.Q. 804, 807 (Bd. Pat. App. & Int. 1982). The references cited above provide more than a reasonable amount of guidance for determining the recognition sequences in the claimed conjugates and describe methods that would be routine to one of ordinary skill in the art.

However, the Examiner stated that the fact that an assay must be performed to find the right peptide sequence supports the Examiner's view that predictability in discovering peptides that are cleavable by specific digestive enzymes is low because the enzyme is selective. **The Examiner has provided no basis for the allegation of lack of predictability, which according to the Examiner is due to the selectivity of the enzyme.** Once the applicant has provided evidence to rebut an allegation, mere assertion on the part of the examiner is insufficient to maintain. Applicants are unclear as to how the Examiner arrived at the conclusion that an assay *must* be performed to obtain the right peptide sequence. The specification states that a variety of methods are known in the art that can be used to determine the cleavage motif of a target enzyme **when it is not yet known** (see page 17, lines 1-2). This is not tantamount to saying that an assay must be performed to identify such sequences. There are no such experiments performed in the present application to obtain sequences for MMP-2 and MMP-9 used in the examples. Clearly,

the Examiner has ignored the numerous target sequences disclosed in Appendix A (Table 1), in Turk, and those which are known in the prior art (admitted by the Examiner, office action page 5), which the specification clearly states are cleavage motifs which can be used as linkers (see page 16, lines 13-19). Applicants additionally disagree with the Examiner's allegation that the Examiner has clearly shown that discovering peptides that are cleavable by specific digestive enzymes claimed is unpredictable. The Examiner has provided no evidence to this effect and has instead relied on a sentence from the present application, while ignoring abundant evidence submitted by Applicants to demonstrate that linkers that can be used as claimed are known (see Turk), are disclosed in the specification (see Table 1 in Appendix A), and that it would be routine experimentation to identify sequences when they are not known for a particular enzyme. Patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

The amount of direction or guidance presented in the application and the quantity of experimentation necessary

The specification discloses that phage display method has been used to determine peptide substrates for a number of proteases, for example, plasmin (Hervio *et al.*, *Chem. Biol.*, 7:443 (2000)); tissue-type plasminogen activator (Ding *et al.*, *Proc. Natl. Acad. Sci. USA*, 92:7627 (1995) and Ke *et al.*, *J. Biol. Chem.*, 272:16603 (1997)); prostate-specific antigen (Coombs *et al.*, *Chem. Biol.* 5:475 (1998)); and membrane type-1 matrix metalloproteinases (Ohkubo *et al.*, *Biochem. Biophys. Res. Commun.*, 266:308 (1999)) (page 17, line 18 to page 18, line 2). These

references disclose several oligopeptides which are substrates for plasmin, plasminogen activator, prostate-specific antigen, and membrane type-1 matrix metalloproteinases. Appendix A lists the cleavage motifs for a range of secreted or membrane bound proteases that are overexpressed in certain tumor tissues.

The specification discloses screening techniques which identify sequences which are labile to the target enzyme but resistant to serum proteins (page 18, lines 16 and 17). The specification discloses methods for making the conjugates as well as assays for evaluating whether a particular linker is suitable for use in a conjugate (*see* the Examples). For example, sets of polymer-linker-drug conjugates or polymer-linker-dye conjugates may be synthesized for kinetic analysis to determine the kinetics of enzyme cleavage (page 19, lines 6-16).

The presence of working examples

Examples 1, 5, 6, 7, and 8 describe the synthesis of dextran-oligopeptide-drug conjugates containing doxorubicin or methotrexate. The oligopeptides were synthesized using conventional solid-phase techniques and the conjugates may be synthesized using traditional techniques of peptide coupling and dextran modification. This methodology can be used to prepare conjugates containing other peptide linkers since peptides generally contain the same or similar functional groups.

Examples 2 and 9 describe the peptidyl release of doxorubicin and methotrexate in the presence of MMP-2. Examples 3 and 10 describe *in vitro* cytotoxicity studies of dextran-oligopeptide-drug conjugates containing doxorubicin and methotrexate. Examples 4 and 11

describe serum stability studies of dextran-oligopeptide-drug conjugates containing doxorubicin and methotrexate. These assays can be used to evaluate the release of an active agent from other peptide linkers, the cytotoxicity of conjugates containing other peptide linkers, and the serum stability of conjugates containing other peptide linkers. The Examiner has provided no evidence that the methods of synthesis and/or assays described in the Examples cannot be used with other peptide linkers.

Conclusion

Applying the *Wands* factors, one sees that the specification provides a high level of detail for the claimed conjugates and methods of making and characterizing thereof. The level of skill in the art is high, and one of ordinary skill in the art is aware of a variety of oligopeptides which are substrates for plasmin, plasminogen activator, prostate-specific antigen, and membrane type-1 matrix metalloproteinases and methods for generating such peptides. The claims are not overly broad. Therefore, one of ordinary skill in the art could make and use the claimed compositions without undue experimentation.

Therefore, claims 1-3, 5, 6, 9-23, 29, 33, 39, 43-49, 51-52, and 54-56 are enabled.

Rejection Under 35 U.S.C. § 112, second paragraph

Claim 4 was rejected under 35 U.S.C. §112 second paragraph for being indefinite. Claim 4 has been cancelled, rendering this rejection moot.

Rejection Under 35 U.S.C. § 102

Claims 1-6, 9-13, 17, 21, 29, 33, 39, 43, 47, 51-52, and 54-55 were rejected under 35 U.S.C. § 102(b) as being anticipated by WO 01/68145 to Copeland *et al.* ("Copeland"). Claims 1, 12 and 13 have been amended to specify that the polymeric carrier the polymeric carrier has a size greater than 6 nm. Support for this amendment can be found in the specification at least at page 9, lines 13-18. Claim 4 has been cancelled. Applicants respectfully traverse this rejection as applied to the amended claims.

Legal Standard

For a rejection of claims to be properly founded under 35 U.S.C. § 102, it must be established that a prior art reference discloses each and every element of the claims. *Hybritech Inc. v Monoclonal Antibodies Inc.*, 231 U.S.P.Q. 81 (Fed. Cir. 1986); *Scripps Clinic & Research Found v. Genentech Inc.*, 18 U.S.P.Q.2d 1001 (Fed. Cir. 1991). The Federal Circuit held in *Scripps*, 18 U.S.P. Q.2d at 1010:

Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. [...] There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention.

A reference that fails to disclose even one limitation will not be found to anticipate, even if the missing limitation could be discoverable through further experimentation. As the Federal Circuit held in *Scripps*:

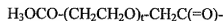
[A] finding of anticipation requires that all aspects of the claimed invention were already described in a single reference: a finding that is not supportable if it is necessary to prove facts beyond those disclosed in the reference in order to meet the claim limitations. The role of extrinsic evidence is to educate the decision maker to what the reference meant to persons of ordinary skill in the field of the invention, not to fill in the gaps in the reference.

Id.

For a prior art reference to anticipate a claim, it must enable a person of ordinary skill in the art to practice the invention. The Federal Circuit held that "a §102(b) reference must sufficiently describe the claimed invention to have placed the public in possession of it. [...] [E]ven if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling." *Paperless Accounting Inc. v. Bay Area Rapid Transit Sys.*, 231 U.S.P.Q. 649, 653 (Fed. Cir. 1986).

Analysis

Copeland describes compositions containing antineoplastic agents conjugated to enzyme cleavable peptides containing the amino acid recognition sequence of a membrane-bound and/or cell secreted peptidase (abstract). The peptide is capped with a capping group (page 5, line 31). Suitable capping groups are discussed beginning at page 42, line 26. Copeland discloses that polyethylene glycols having the formula



Where t is 1 to 10, preferably t is 1, 2, 3, or 4, more preferably where t is 1 or 2 can be used as amino-capping groups (page 43, lines 17-22). Copeland states that unless otherwise specified, "polyethylene glycol", or "PEG" or "Peg" as an amino capping group having the formula shown below (page 43, lines 20-22):



This molecule contains only two monomer units.

The specification at least at page 9, lines 13-18 for example, disclose that macromolecules with sizes above 6 nm (MW ~ 50,000 Da) exhibit marked inhibition on renal clearance. PEG with $n = 80$ would have an average molecular weight of 3500 Da (see http://en.wikipedia.org/wiki/Polyethylene_ glycol, retrieved on June 9, 2008, a copy of which is attached). It is clear that the PEG end capping units disclosed in Copeland, which contain between 2 and 10 monomer units, are outside the scope of the claimed conjugates.

Accordingly, claims 1-6, 9-13, 17-22, 29, 33, 39, 43, 47-52, and 54-56, as amended are novel over Copeland.

Rejection Under 35 U.S.C. § 103

Claims 1-6, 9-14, 17, 18, 21, 22, 29, 33, 39, 43, 44, 47-48, 51-52, and 54-56 were rejected under 35 U.S.C. § 102(b) as unpatentable over WO 98/56425 to Duncan ("Duncan"), in view of Copeland. Applicants believe the Examiner intended to say the claims were rejected under 35 U.S.C. § 103(a), instead of 102(b), and will present arguments accordingly. Applicants

respectfully traverse the rejection of the claims under 35 U.S.C. § 103(a) as applied to the amended claims.

Legal Standard

Obviousness is a legal conclusion based on underlying facts of four general types, all of which must be considered by the examiner: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) any objective indicia of nonobviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 USPQ 459 (1966). This standard was recently affirmed by the Supreme Court in *KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385 (2007). The Court did not totally reject the use of "teaching, suggestion, or motivation" as a factor in the obviousness analysis. Rather, the Court recognized that a showing of "teaching, suggestion, or motivation" to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a).

The Supreme Court did not obviate the requirement for the references to provide some motivation to combine as applicants have done, with a reasonable expectation of success. Indeed, the examiner's attention is drawn to the following quote by the Court in *KSR*:

"The TSM test captures a helpful insight: A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art. Although common sense directs caution as to a patent application claiming as innovation the combination of two known devices according to their established

functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the art to combine the elements as the new invention does. Inventions usually rely upon building blocks long since uncovered, and claimed discoveries almost necessarily will be combinations of what, in some sense, is already known. . . . There is no necessary inconsistency between the test and the *Graham* analysis."

"Focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness." *Gillette Co. v. S.C. Johnson & Sons, Inc.*, 919 F.2d 720, 724, 16 U.S.P.Q.2d 1923 (Fed. Cir. 1990); see *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1383, 231 U.S.P.Q. 81, 93 (Fed. Cir. 1986). "One cannot use hindsight reconstruction to pick and choose among isolated disclosures on the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988).

Analysis

As discussed above, the United States Supreme Court in *KSR* reaffirmed the *Graham* factors an obviousness analysis. The *Graham* factors are analyzed below:

(a) Determining the scope and contents of the prior art

Duncan

Duncan describes a product or kit containing two components, i.e., two pharmaceutical compositions that are arranged or otherwise adapted for sequential administration to a human or animal (page 3, line 36 to page 4, line 2). The first component is an enzyme conjugate, e.g., a

composition that contains a pharmaceutically acceptable excipient and an enzyme conjugate (page 4, lines 2-5). The enzyme conjugate may consist of an enzyme covalently bound to a polymeric or other carrier, such that the enzyme conjugate retains its enzyme activity (page 4, lines 5-7). The second component is a prodrug, e.g., a composition that contains a pharmaceutically acceptable excipient and a prodrug (page 4, lines 8-10). The prodrug can be conjugated to a polymeric carrier via a peptide linker (page 10, lines 9-10).

Copeland

Copeland is discussed above.

(b) Ascertaining the differences between the prior art and the claims

A combination of Duncan and Copeland does not disclose all of the claim elements as required by a rejection under 35 U.S.C. 103(a). While the Examiner admitted that Duncan is silent on linkers are digested by serine proteases and matrix metalloproteases overexpressed by a tissue, the Examiner cited to Copeland for providing enzyme-cleavable peptides including recognition segments for MMP-2. However, a combination of Duncan and Copeland is impermissible because Copeland teaches away from the polymeric carriers required by the claims.

A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. The degree of teaching away will of course depend on the particular facts; in general, a reference will teach away if it

suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant. See *United States v. Adams*, 383 U.S. 39, 52, 148 U.S.P.Q. (BNA) 479, 484, 15 L. Ed. 2d 572, 86 S. Ct. 708 (1966) ("known disadvantages in old devices which would naturally discourage the search for new inventions may be taken into account in determining obviousness"); *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1550-51, 220 U.S.P.Q. (BNA) 303, 311 (Fed. Cir. 1983) (the totality of a reference's teachings must be considered), cert. denied, 469 U.S. 851 (1984); *In re Caldwell*, 50 C.C.P.A. 1464, 319 F.2d 254, 256, 138 U.S.P.Q. (BNA) 243, 245 (CCPA 1963) (reference teaches away if it leaves the impression that the product would not have the property sought by the applicant).

As discussed above, Copeland describes conjugates containing an anticancer agent and an enzyme-cleavable peptide linker. The linker can be **optionally modified** at the end not conjugated by the drug, typically the N-terminus (page 42, lines 19-22). Copeland discloses that such modifications can be for a number of reasons, for example, to increase plasma stability of the peptide against enzymatic degradation by non-selective enzymes in the plasma or to increase solubility (page 42, lines 22-24). Suitable capping groups include PEG oligomers, where the number of monomer units is from 1 to 10.

A capping group containing an oligomer of PEG described in Copeland are not sufficiently large as required by the claims. A reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant. The oligomers disclosed in Copeland are not likely to be

productive of the result sought by the applicant. Accordingly, one would not be motivated to combine the conjugates of Duncan with the oligomers of Copeland to arrive at the claimed compositions.

With respect to the method of administration claims, one of ordinary skill in the art would not be motivated to combine Duncan and Copeland because Duncan teaches away from administering a conjugate containing a linker that is cleaved by a digestive enzyme overexpressed by the tissue itself.

As discussed above, Duncan discloses the sequential administration of a prodrug conjugate with an enzyme conjugate. The enzyme conjugate is administered in order to achieve overexpression of the enzyme at the desired site of release of the prodrug. In contrast, the claimed compositions contain a linker containing an oligopeptide recognition segment that is cleaved by a digestive enzyme that is overexpressed *by the tissue*. Duncan teaches away from the claimed compositions and methods since Duncan leaves the impression that one must co-administer an enzyme conjugate in order to achieve overexpression and cleavage of the peptide linker. The MPEP §2143.01 is clear that a proposed modification cannot render the prior art unsatisfactory for its intended purpose or change the principle of operation of a reference.

(c) Secondary Considerations of Obviousness

Secondary considerations to be considered include commercial success, long felt but unresolved needs, failure of others, unexpected results, etc.

The results shown in Example 12 (discussed below) are unexpected in view of the teachings of Duncan which requires the co-administration of an enzyme conjugate in order for the drug conjugate to be effective and are strong indicia of non-obviousness.

Example 12 describes the *in vivo* evaluation of the anti-tumor efficacy of dextran-oligopeptide-methotrexate conjugates. Six week old female SCID mice were injected with IIT-1080 tumor cells. Free methotrexate, dextran-oligopeptide-methotrexate, or dextran-methotrexate was injected intraperitoneally on day 1, 8, and 15 after a tumor was first established. Weight and tumor size were monitored three times a week. The average tumor size was suppressed 92% by the dextran-oligopeptide-methotrexate and dextran-methotrexate compared to untreated animals (PBS), which was 44% more than the suppression seen with free methotrexate. Linking methotrexate to a polymeric carrier, such as dextran, increases the half-life of the drug by decreasing renal elimination rendering the benefit of passive targeting. **The presence of a peptide linker containing a recognition segment promotes cleavage of the conjugate in the extracellular space of the tumor tissue where the digestive enzyme is overexpressed with decreased side effects.**

The Examiner's attention is drawn to the specification at least at page 59, which discloses that dextran-methothrexate, albeit showing promising efficacy, was significantly more toxic than dextran-oligopeptide-methothrexate. Thus, not only do the claims provide a drug conjugate and a method of administering the drug conjugate that eliminates the

need for an additional conjugate containing an enzyme as required by Duncan, this method of treatment is associated with decreased toxicity.

Allowance of claims 1-3, 5, 6, 9-56, as amended, is respectfully solicited.

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